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Appl. No. 09/764,163
Amdt. dated April 16, 2007
Reply to Office Action of December 15, 2006

REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

With entry of this amendment claims 86 is canceled. Claims 80, 84, 85, 87-88, and 90-97 are pending. Claims 80, 84, and 85 are amended and claims 90-97 are new.

The amendments to the claims are made soley in an effort to expedite prosecution of the application. Applicants reserve the right to pursue the broader and/or canceled claims in a continuation application without prejudice. No new matter is added with entry of this amendment.

Claim Amendments

Claims 80 and 84 are amended to correct the use of "break-point" so as to be consistent with the specification and as requested by the Examiner. Line 2 of claim 80 is amended to recite "a first and a second interactor domain, and..." to provide antecedent basis for the second interactor domain. Claim 80 is also amended to recite that the circularly permutated β-lactamase is a TEM-1 β-lactamase protein. Support for the TEM-1 β-lactamase protein can be found throughout the specification, for example, in the abstract.

Substantively, claim 80 is amended to include Markush groups from which the first and second interactor domains can be selected. Support for the members of the Markush groups can be found throughout the specification, for example, support for antibody-antigen interactions can be found in Example 11b (paragraph [0155]) of the Pre-Grant Publication. Support for an antibody and a scaffold peptide can be found in paragraph [0035] which states "...a natural or synthetic antibody repertoire such as a single chain variable region library or a light chain variable region library, or a randomly generated peptide library presented in the context of thioredoxin." Similarly, paragraph [0074] discloses the use of scaffold proteins to isolate surrogate ligands for proteins and for antigen epitope mapping of antibodies. Paragraph [0072] provides support for the use of hetero-dimerizing helices, while paragraph [0048] provides specific support where the monomers are c-fos and c-jun. Additional support for the members of the Markush groups can be found throughout the specification, including paragraphs [0025], [0048], [0053], [0057], [0070-0076], [0151], Examples 2 and 11, and figure 11 of the

Pre-Grant Publication. These same passages, in particular figure 11, and example 11, provide support for newly added claims 90-97.

Claim 80 is also amended to restrict the location for the N-terminal and C-terminal break-point to within 10 amino acids in either direction from a junction of 2 amino acid residues located between alpha-helices 7 and 8 of the TEM-1 β-lactamase protein. Support for this amendment can be found throughout the specification, for example, in paragraph [0049] of the Pre-Grant Publication. Dependent claim 85 is amended to be consistent with claim 80 as presently amended, and claim 86 is canceled.

II. PROVISIONAL DOUBLE-PATENTING REJECTION

Claims 80, and 84-88 stand provisionally rejected under the judicially created doctrine of double-patenting as allegedly being obvious over claims 63-74 of co-pending U.S. Application No. 10/668,778.

Applicants disagree.

First, claim 86 is canceled, rendering the rejection to claim 86 moot. Second, Applicants note that MPEP §804(I)(B)(1) states that "[I]f a 'provisional' nonstatutory double patenting (ODP) rejection is the only rejection remaining in the earlier filed of two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

With regard to the pending claims, Applicants respond by noting that claims 63-74 of co-pending Application No. 10/668,778 do not teach or suggest **a single polypeptide** containing a first interactor domain and a second interactor domain. Nor do claims 63-74 teach or suggest the use of **a circularly permutated** β-lactamase protein. Rather, claims 63-74 set forth a fragment complementation system comprising **a first oligopeptide** comprising an N-terminal fragment of a β-lactamase protein covalently bonded through the C-terminal break-point to a first interactor domain; and **a second oligopeptide** comprising a C-terminal fragment of a β-lactamase protein covalently bonded through the N-terminal break-point to a second interactor domain.

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Because claims 63-74 of co-pending U.S. App. No 10/778,668 do not teach or suggest all of the salient elements of the presently claimed invention, withdrawal of the rejection is respectfully requested.

III. CLAIM OBJECTION

Claim 84 is objected to for the informality that the claim recites "break point" whereas the antecedent "breakpoint(s)" in claim 80 is one word. Correction is required.

Applicants have amended claims 80 and 84 to replace "breakpoint" or "break point" with "break-point" to be consistent with the specification.

In view of the claim as presently recited, Applicants request that the Examiner withdraw the objection.

IV. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

A. Written Description

Claims 80, and 84-88 stand rejected under 35 U.S.C. §112, First paragraph as failing to comply with the written description requirement. The Examiner alleges that the specification is broadly drawn to a circularly permutated β-lactamase protein where the first interactor domain is fused to the circularly permutated β-lactamase through the N-terminal break-point and a second interactor domain is fused to the circularly permutated β-lactamase through the C-terminal break-point. The Examiner alleges that the interactor domains are taken as including species which interact with *known* as well as *unknown* ligands. *See*, page 5 of the Office Action, referring to page 11 of the specification. The Examiner alleges that a skilled artisan could not envision what kinds of unknown interactor domains are truly capable of re-folding β-lactamase and therefore be included as part of the claimed genus. *See*, page 5 of the Office Action. Specifically, the Examiner alleges that the Applicant has not provided functional characteristics coupled with a known or disclosed correlation between function and structure for known interactor domains which are compatible with the claimed invention (see, page 5 of the Office Action). In support of the argument, the Examiner provides an example where a single

amino acid (e.g. tryptophan) could be considered a small interactor domain since it interacts with tryptophan synthetase, but does not understand how a single residue would reconstitute the β-lactamase. To the extent that the rejection applies to the currently amended claims, Applicants traverse the rejection.

The law with regard to written description clearly states that it is **not necessary** that the specification describe claim terms **exactly**, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that the applicants invented the composition including those terms. *See, In re Wertheim*, 191 USPQ 90, 96 (CCPA 1976); *Ralston Purina Co., v. FarMar-Co., Inc.* 227 USPQ 177, 179 (Fed. Cir. 1985), stating that the test for support of the subject matter of a claim is whether the disclosure of an application "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter" (quoting *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir 1983)). The MPEP sets forth the principle that "Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification." *See*, MPEP §2163(II)(A)(2) citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). Interactor domains suitable for use with the present invention, encompass a variety of diverse embodiments. This diverse nature of the interactor domains makes clear that the interactor domains are not constrained by common functional or structural characteristics. Furthermore, the specification describes numerous embodiments of interactor domains that exemplify their diverse nature as presently claimed.

A skilled artisan reading the application as filed would understand that a known or unknown interactor domain can include an antibody (*e.g.*, an scFv antibody), a heterodimerizing duplex (*e.g.*, fos/jun monomers) and a scaffold peptide (*e.g.*, CD40 trxpeps as described in example 11 of the specification). Furthermore, a skilled artisan would recognize that each of these known or unknown interactor domains can be members of a library. Specific examples of such libraries are presented in paragraph [0035] of the Pre-Grant Pub. (US 2003/0165825) which states:

> The first interactor domain is a known or unknown protein or protein fragment that binds…to a second target interactor domain that is an unknown protein or protein fragment and either or both the first and second interactor domain can be a member of a library…. The libraries can encode any representative synthetic or naturally occurring polypeptide population of interest. For example, a library can represent the entire proteome of a cell of interest, or a natural or synthetic antibody repertoire such as single chain variable region library or a light chain variable region library, or a randomly generated peptide library presented in the context of thioredoxin….

As is made clear by the above passage, a skilled artisan reading the application as filed would understand that the first and second interactor domains are **proteins or protein fragments** and that either or both of the first and second interactor domains can be **members of a library**. Moreover, the claims as presently recited are drawn to embodiments with the interactor domains selected from members of a Markush group. Notably, a single amino acid (*e.g.*, tryptophan) does not fall within the scope of the interactor domains as presently claimed.

In view of the arguments as presented above, and the claims as currently recited, the Applicants request that the Examiner withdraw the rejection.

B. Enablement

Claims 80, 85, 86, and 88 stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. Specifically, the Examiner acknowledges that the specification is enabling for circularly permuted β-lactamase comprising N and C interactor domains with a breakpoint between Glu197 and Leu 198, but alleges that it does not reasonably provide enablement for the other breakpoints set forth in claims 85 and 86. In supporting the assertion that the application is not enabled for breakpoints other than Glu197 and Leu 198, the Examiner cites to the *Wand* factors (*see, In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). To the extent that the rejection applies to the claims as currently amended, the Applicants traverse the rejection. In an effort to expedite prosecution of the application, Applicants have amended independent claim 80 to be consistent with that which the Examiner has acknowledged the application is enabled. Specifically, the claims are now restricted to a breakpoint within 10

amino acids in either direction form a junction of 2 amino acid residues located between alpha-helices 7 and 8 of a TEM-1 b-lactamase protein. This region between alpha-helices 7 and 9 extends approximately from Thr 195 to Ala 202, and includes Glu 197 and Leu 198. The specification provides ample evidence that the claims are enabled using a break-point that falls within the recited loop. *See*, paragraph [0049] of the Pre-Grant Publication.

In light of the above, the Applicants request that the Examiner withdraw the rejection.

V. REJECTION UNDER 35 U.S.C. §102

Claims 80 and 84 stand rejected under 35 U.,S.C. §102(b) as allegedly anticipated by Pieper *et al.* (1997) *Biochemistry* 36:8767 (IDS entry 5/5/2004). *See*, page 9, of the Office Action. Specifically, the Examiner cites the claimed invention as consisting essentially of a first and second interactor domain as described *supra*. The Examiner alleges that claim 84 adds the limitation that the N-terminal and C-terminal breakpoint are in a solvent exposed loop between elements of secondary structure. Furthermore, the Examiner cites Pieper *et al.*, as teaching a circularly permutated β-lactamase joined at the native N and C termini, through a linker peptide, and a new N and C termini established between Gly253 and Lys 254 (cp254) or Ala227 and Gly228 (cp228). *See*, page 10, of the Office Action.

Applicants traverse the rejection. The Examiner's non-conventional view of Pieper *et al.* alleges that the N-terminal fragment of the β-lactamase protein can function as a first interactor domain, and the C-terminal fragment of the β-lactamase protein as a second interactor domain. Applicants disagree. Pieper *et al* teaches that the peptide linker is attached to the *native* N-terminal and the *native* C-terminal ends to generate a circularly permutated protein, and then introducing NEW termini at a break-point in a solvent exposed loop. Pieper *et al.*, however, does not teach the attachment of interactor domains to the newly created N- and C-termini at the breakpoint, as presently claimed. Specifically, Pieper *et al.* does not teach or suggest a first and a second interactor domain *fused* to the circularly permutated β-lactamase protein *through* the N-terminal and C-terminal *break-points* of the circularly permutated β-lactamase protein as presently claimed. Because does not teach the attachment of a first and

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second interactor domain to the newly created N-termini and C-termini at the breakpoint in the solvent exposed loop Pieper *et al.* does not anticipate the invention as presently claimed.

Furthermore, Pieper *et al.* teaches three constructs, none of which teaches or suggests the introduction of a breakpoint between helices 7 and 8 as presently claimed. *See*, page 8770, second column, of Pieper *et al.* Because Pieper *et al.* does not teach or suggest all of the salient elements of the invention as presently recited, Pieper et al. does not anticipate the invention.

In view of the above, Applicants request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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